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Original Article

Externally validated digital decision support tool for time-to-osteoradionecrosis risk-stratification using right-censored multi-institutional observational cohorts

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ABSTRACT

Background: Existing studies on osteoradionecrosis of the jaw (ORNJ) have primarily used cross-sectional data, assessing risk factors at a single time point. Determining the time-to-event profile of ORNJ has important implications to monitor oral health in head and neck cancer (HNC) long-term survivors.
Methods: Data were retrospectively obtained for a clinical observational cohort of 1129 patients (198 ORNJ cases) with HNC treated with radiotherapy (RT) at The University of Texas MD Anderson Cancer Center. A Weibull Accelerated Failure Time model was trained on previously identified dosimetric, clinical and demographic predictors. External validation was performed using an independent cohort of 265 patients (92 ORNJ cases) treated at Guy's and St. Thomas' Hospitals. To facilitate clinical implementation of the model, an online graphical user interface (GUI) was developed, including formal stakeholder usability testing.
Results: Our model identified that gender (males), pre-RT dental extractions and D25% were associated with a 38 %, 27 % and 12 % faster onset of ORNJ, respectively, with adjusted time ratios of 0.62 (p = 0.11), 0.73 (p =

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0.13) and 0.88 ($p < 0.005$). The model demonstrated strong internal calibration (integrated Brier score of 0.133, D-calibration p-value 0.998) and optimal discrimination at 72 months (Harrell's C-index of 0.72).
Conclusion: This study is the first to demonstrate a direct relationship between radiation dose and the time to ORNJ onset, providing a novel characterization of the impact of delivered dose and patient-related factors not only on the probability of a late effect (ORNJ), but the conditional risk during survivorship.

Introduction

Osteoradionecrosis of the jaw (ORNJ) is a severe iatrogenic sequela of radiotherapy (RT) that impacts patients treated for head and neck cancer (HNC) at an estimated prevalence of 4–15 % [1]. Radiation-associated devascularization of bone and normal tissue injury lead to loss of cortical bone integrity which fails to heal, resulting in a constellation of symptoms that substantially reduce quality of life and limit oral function [2,3]. The lack of early detection methods and risk assessment tools for ORNJ make prevention and detection difficult for medical professionals to preemptively manage the condition, often delaying care and resulting in costly, invasive interventions.

Patients are at a lifetime risk of developing ORNJ following RT, which is of increased concern for patients who are now living much longer following RT for HNC. The explosive growth of human papilloma virus-associated (HPV +) oropharyngeal cancer (OPC) often affecting non-smokers has resulted in more long-term survivors of patients treated with radiation for HNC. For this reason, determining the long-term (>2 year) time-to-event profile of ORNJ has important implications for professionals who may be monitoring the oral health of long-term survivors for many years after intensive disease surveillance has transitioned to survivorship [4].

Numerous studies [5–9] have examined the statistical correlation between ORNJ and various dosimetric, clinical, and demographic risk factors. In a previous investigation [10], we pioneered and externally validated the first ORNJ Normal Tissue Complication Probability (NTCP) model. While these investigations offer invaluable insights that steer clinical decision-making and treatment plan optimization, they largely rely on cross-sectional datasets, where the potential for reporting bias exists, and do not account for right-censoring (i.e., consideration of cases without event or who are under surveillance and have not had ORNJ but remain at risk). As Van den Bosch et al. [11] note "NTCP-models are generally developed for a single complication grade at a single time point", thus overlooking the temporal variability in toxicity risk.

Understanding the influence of treatment decisions and risk factors on the timing of ORNJ is crucial for effective prevention and management. Treister et al. [12] carried out risk factor association analysis on a longitudinal ORNJ data set with d ata points at 6, 12 and 24 months and identified pre-RT extractions, higher RT dose and tobacco use as significant risk factors. The present study aims to model longitudinal associations to provide patient-specific ORNJ risk predictions over time. Widely used non-parametric and semi-parametric models, such as Cox proportional hazard, may not fully capture the nuanced temporal dynamic of the event due to their broader assumptions about data distribution. Accelerated Failure Time (AFT) models offer a valuable parametric alternative, which enhances the interpretability of each factor's influence on the event onset. Weibull models are especially attractive as a parametric approach for time-to-event applications for risk-prediction [13–15] as an interpretable alternative to the clinically familiar non-parametric proportional hazards methods.

As part of a larger effort to leverage right-censored models to inform risk-based surveillance and prophylactic management trial enrolment [16], as well as considering challenges to traditional NTCP models [17], we have sought to undertake the following specific aims:

i) Determine relative actuarial incidence of ORNJ over time, ii) derive and externally validate a dose-aware actuarial time-to-event NTCP models for ORNJ that incorporates right-censored clinico-demographic factors for patient risk stratification and iv) develop and test an online clinical decision support tool with a graphical user interface (GUI) for clinical implementation of the risk model, including formal stakeholder usability testing.

Methods

A multivariable time-to-event prediction model was developed on an internal dataset from MD Anderson Cancer Centre (MD Anderson) and externally validated on an independent cohort of a British population treated at Guy's and St Thomas' NHS Foundation Trust (GSTT). Analysis was performed as per reporting guidelines [18] (Supplement A).

Patients

After institutional review board approval (RCR030800), data from a philanthropically funded observational cohort (Stiefel Oropharynx Cancer Cohort, PA14-0947) were extracted for retrospective acquisition. Patients in the internal MD Anderson cohort included all consented RT cases treated with curative intent from 2005 to 2022; patients with prior RT (i.e., re-irradiation) were excluded. Patients undergoing RT for HNC are closely followed up with clinical and radiological assessments every 3 to 6, 12, 18 to 24 months then approximately annually after the end of the RT course. An external cohort was obtained retrospectively from the HNC clinical database maintained at GSTT under the Northwest – Haydock Research Ethics Committee of the NHS Health Research Authority (REC reference 18/NW/0297, IRAS project ID: 231443); patients treated between 2011 and 2022 were included. The GSTT clinical protocol for HNC patients includes clinical follow up for up to five years post-RT. Control subjects in the GSTT cohort were retrospectively matched with a 2:1 ratio based on primary tumor site and treatment year. Incomplete or not available datasets were excluded.

Clinical endpoint

The primary analysis framework focused on ORNJ as the sole event of interest. The primary endpoint was defined as the development of any physician-reported grade of ORNJ following the initiation of RT (i.e., ORNJ vs. no ORNJ), with the time to event (TTE) recorded as the interval (in months) from the start date of RT to the first documented instance of ORNJ in the patient's electronic medical health record. As the current datasets pre-date recent consensus recommendations [19,20] and used then-institutional standard clinical reporting, we designated all cases as ORNJ; this was necessary as divergent ORNJ grading systems (Tsai [21]/Notani [22]) were in-use. Patients without confirmed ORNJ diagnosis were right censored at the date of last contact.

Statistical analyses

Weibull AFT model development

Upon revision of the cohort and subsequent updating of our previously developed [10] ORNJ NTCP model (Supplement B), a multivariable time-to-event ORNJ prediction model was developed using the Weibull probability distribution.

A Weibull distribution is characterized by two main parameters: a scale parameter (λ), determining the distribution spread over time, and shape parameter (ρ) which indicates whether the rate of the event

increases ($\rho > 1$), decreases ($\rho < 1$), or remains constant ($\rho = 1$) over time. Considering covariates X_1, X_2, … X_n, the function of the scale parameter can be expressed as $\lambda(x) = \exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n)$, where β_0 is the intercept of the transformed scale when all covariates are at their reference level, while β_1, β_2, …., β_n are the coefficients of the log-linear relationship between each covariate and the time to event [23–26]. The corresponding survival function for the Weibull AFT model is articulated as $S(t;x) = \exp\left(-\left(\frac{t}{\lambda(x)}\right)^{\rho}\right)$, where $S(t;x)$ represents the probability of a patient surviving beyond time t without experiencing ORNJ, given their specific covariates x.

Considering β_{D25}, β_{gender}, and β_{dental} the coefficients of the covariates $D_{25\%}$ (X_{D25}), gender (X_{gender}), and pre-RT tooth extraction (X_{dental}), respectively (see Supplement B), on the log-transformed time to ORNJ, the function of the scale parameter, pertinent to our study, is thus expressed as $\lambda(x) = \exp\left(\beta_0 + \beta_{D25} X_{D25} + \beta_{gender} X_{gender} + \beta_{dental} X_{dental}\right)$.

Adjusted Time Ratios (ATRs), calculated as the exponential of regression coefficients, were used to interpret the proportional impact of the model's covariates on the time to ORNJ for one unit increase in continuous variables or in relation to reference group(s) in categorical ones.

The analysis and WAFT model development was conducted in Python programming environment (version 3.11) using the '*WeibullAFTFitter*' function of the *Lifelines* (version 0.28) survival analysis library [27].

AFT Model evaluation

The Weibull AFT model was internally and externally validated. For internal validation, the dataset was randomly split into training (80 %) and test (20 %) subsets with balanced ORNJ status representation. Model performance was assessed in terms of overall performance, predictive accuracy and model calibration on both the internal and external datasets using time-independent metrics [28]. In the context of time to event analysis, the Integrated Brier score (IBS) provides a single summary measure of the model's prediction accuracy over time. The concordance index (Harrell's C-index) was used to measure the predictive accuracy of the model in terms of its ability to correctly rank the event times. Model calibration was assessed with the Distributional calibration (D-calibration), which is a measure of the calibration of the predicted survival curves.

GUI development and prospective assessment

The WAFT-based time-to-ORNJ online calculator graphical user interface (GUI) is available at https://uic-evl.github.io/OsteoradionecrosisVis/ (Fig. 1). The usability of the GUI was prospectively evaluated on a test dataset by 25 users of different degrees of expertise and clinical specialties. A Qualtrics survey was designed with eight case-specific questions, the ten questions from the Brooke et al. [29] SUS scale questionnaire and three additional open questions for additional feedback.

Results

From a population of 1259 MD Anderson patients with HNC, a total of 1129 patients were included in the final analysis. ORNJ was observed in 198 cases at the end of follow-up period, with a median time to event of 20.5 months (IQR 35.1). The median follow-up time for the censored group was 71.7 months (IQR 62.7). Actuarial time-to-event is shown in Fig. 2. The external validation GSTT cohort consisted of 92 ORNJ subjects and 173 matched controls. The median time to ORNJ was 13.6 months (IQR 20.3) and the median follow-up time for the control group was 47.3 months (IQR 24.2). Further details on the demographic and clinical characteristics of both cohorts can be found in Supplement C.

The ORNJ Weibull AFT (WAFT) model was trained and tested considering the entire time-to-event range in the MD Anderson cohort. Details of the WAFT model are provided in Table 1 and the resulting survival curves stratified by variable are represented in Fig. 3. The shape parameter of the model ($\rho \approx 0.81$) indicated a decreasing hazard rate for ORNJ over time among the study group. For the covariates, our findings suggested that each unit increase in $D_{25\%}$ was significantly associated with an 12 % shorter time to ORNJ (ATR 0.88, $p < 0.005$). We also observed that patients who underwent dental extractions experienced ORNJ at a rate 27 % faster (shorter time to ORNJ) compared to those who did not undergo pre-RT dental extractions (ATR 0.73, $p = 0.13$). A 38 % (ATR 0.62, $p = 0.11$) shorter time to ORNJ was observed in male patients. However, statistical significance of the dental extractions and gender variables was not conclusive.

Maximum discrimination performance of the model at internal validation (Harrell's C-score of 0.723) was observed at the 72 months predictive horizon (Fig. 4a), which coincides with the timepoint where both groups, ORNJ and censored, exhibited the largest difference in the test dataset (supplementary Fig. D1b). Model calibration at internal

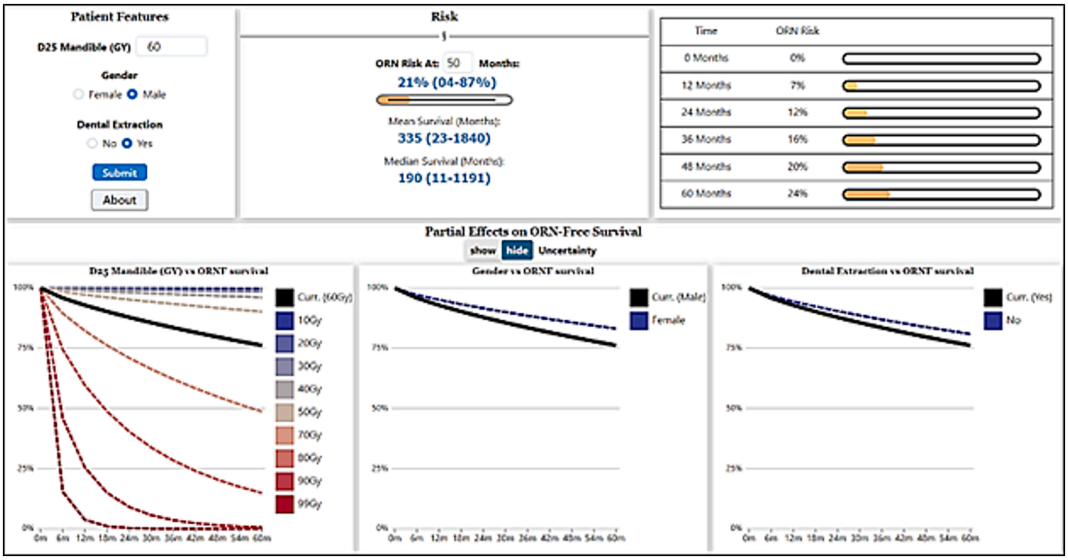


Fig. 1. Screenshot of the WAFT-based time-to-ORNJ online calculator GUI. The user can either obtain a predicted risk of developing ORNJ at a specific time point or visually assess the time-dependency of ORNJ risk with the different covariates of the ORNJ WAFT model.

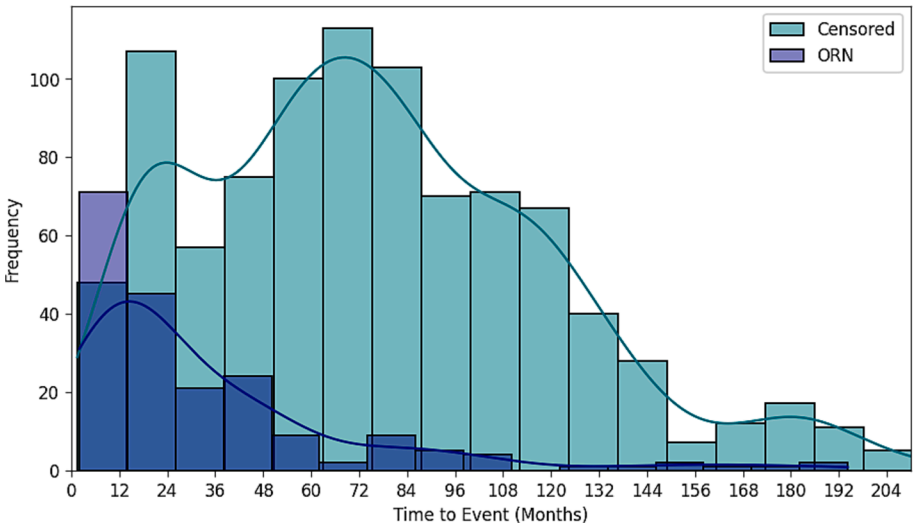


Fig. 2. Frequency plot of actuarial time-to-event in months by ORNJ status for the MD Anderson dataset, where cases with diagnosed ORNJ are in blue and censored (either death or last follow-up) cases are in green; note that deeper blue also corresponds to ORNJ cases but with frequency bars overlapping with those of the censored group. Supplement D includes frequency plots for the training (Fig. D1a), test (Fig. D1b) and external (Fig. D1c) datasets separately. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
ORNJ WAFT model parameters and coefficients.

Parameters	Covariates	Coefficients β_i (95 % CI)	ATR (95 % CI)	p-value
Scale (l)	D25%	−0.12 (−0.15, −0.10)	0.88 (0.86, 0.91)	<0.005
	Dental extractions	−0.31 (−0.71, 0.10)	0.73 (0.49, 1.10)	0.13
	Gender	−0.48 (−1.08, 0.11)	0.62 (0.34, 1.12)	0.11
	Intercept	13.69 (11.77, 15.62)		
Shape (*r*)	Intercept*	−0.21 (−0.35, −0.08)		

* The shape parameter (ρ) is calculated as the exponential of this intercept, resulting in $\rho = e - 0.21 \approx 0.81$.

validation was good to excellent, with an integrated Brier score (IBS) of 0.133 (Fig. 4b) and, as shown in Fig. 4c, successfully d-calibrated (p-value 0.998 > 0.05). Model performance decreased slightly when tested externally on the independent dataset (Supplement E). The distributional calibration plot (supplementary Fig. E1c) shows that the model's predicted probabilities were consistently low compared to the actual outcomes, i.e., the model was underconfident in its predictions.

Overall, the tool was appreciated for its ease of use, but, according to the survey participants, improvements in terminology, layout, response validation, and customization options would enhance its functionality and user experience. The overall average System Usability Scale (SUS) score received was 85.0 (40.0–100.0); a score above 69 is considered above average usability [29]. Except for the Oral Surgery group (mean SUS score 57.5, range 55.0–60.0) all other specialty groups scored the usability GUI above average (Fig. 5). The SUS score increased with number of years of experience (supplementary Fig. F3) except for the group with 15–20 years of experience; this group was composed of four participants, two of which were the Oral Surgeons in the survey. Interestingly, the Oral Surgery specialty group scored the lowest case-specific response accuracy across all specialty groups (supplementary Fig. F1). An extended report on the results of the SUS survey can be found in Supplement F.

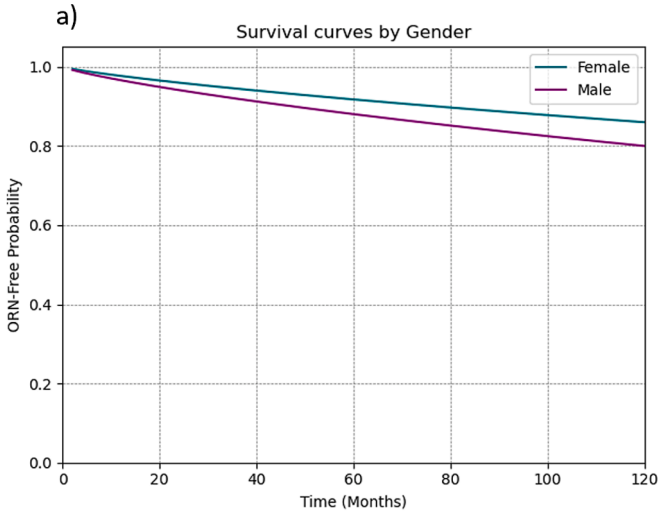
Discussion

In this study, we have successfully developed a novel time-to-event approach for predicting ORNJ, thus providing a more comprehensive estimation of disease trajectory to allow effective risk stratification and surveillance strategies. Our work demonstrates for the first time a direct relationship between radiation dose and the time to development of ORNJ and is a novel characterization of the impact of risk factors not only on the probability of a late effect (ORNJ), but the conditional risk during survivorship. Additionally, we have developed and tested a WAFT-based time-to-ORNJ online calculator graphical user interface (GUI) with overall high usability scoring (Supplement F) that will facilitate clinical implementation of our model.

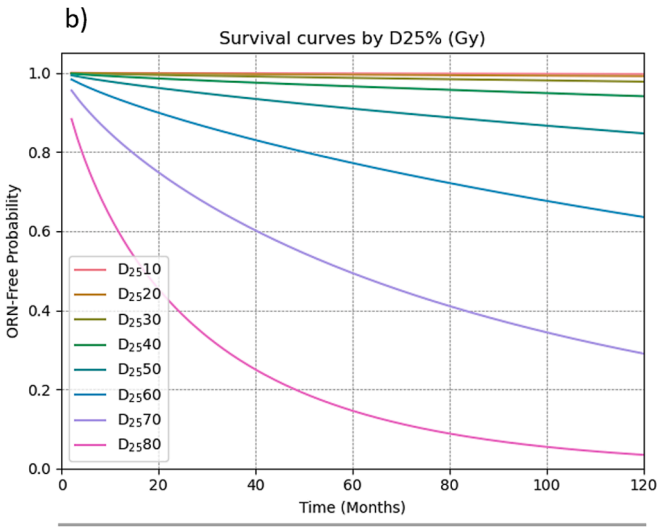
ORNJ is an orphan disease [30] with a currently undefined prevalence, owing to variability in disease classification and, until 2023, lack of a formal International Classification of Disease specific designation (ICD-10 FB81.5), previously denoted as "Other osteonecrosis" without attribution to radiation therapy (ICD-10-CM Diagnosis Code M87.8). Historically, ORNJ (i.e., FB81.5 Osteonecrosis due to ionizing radiation & Specific anatomy:XA51B7 Mandible) has had over 20 distinct descriptive categories, grading systems, or diagnostic criteria. This ambiguity has led to highly variable estimates of the prevalence of ORNJ, with reports designating between 4–15 % [1] of HNC RT cases.

The actual time course of development of ORNJ also remains underdescribed. Using a more restricted criteria of "exposed bone", the most reliable cross-sectional cohort analysis of post-radiation events [12] showed, in 572 longitudinally followed participants, a cumulative rate of exposed bone of 6.1 %, with all patients presenting with disease in < 18 months; however, this high-quality dataset followed patients only until 24 months post-therapy. Other studies report varying median time-to-event, with clinical features such as oropharyngeal disease site [31] or dental extractions [32] associated with faster progression to ORNJ. However, formal toxicity modeling of the conditional probability of ORNJ has not been established until now.

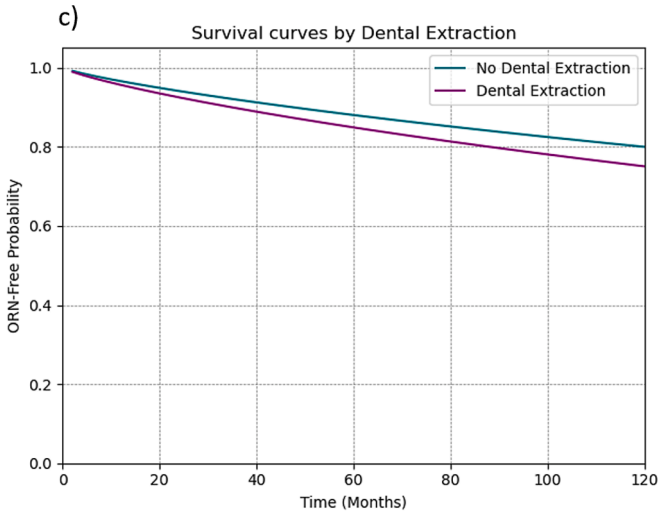
In a previous study [10], a traditional NTCP model was developed, demonstrating a corollary model using the received dose to 30 % or more of mandibular regions of interest (mandible $D_{30\%}$) and pre-radiotherapy dental extraction as predictors of ORNJ. For the current study, prior to the time-to-event model development, we repeated the NTCP modelling exercise after careful manual revision of the dataset (Supplement B). Reassuringly, $D_{25\%}$ (close to $D_{30\%}$) and pre-RT dental



Number of patients at risk							
	0	20	40	60	80	100	120
Male	754	628	518	398	267	178	95
Female	149	118	99	82	62	44	27



Number of patients at risk							
	0	20	40	60	80	100	120
10Gy	41	33	29	22	15	10	8
20Gy	19	12	11	11	7	5	3
30Gy	31	27	22	17	12	7	3
40Gy	119	109	89	71	37	21	15
50Gy	312	288	245	195	146	101	55
60Gy	307	238	198	145	100	70	34
70Gy	74	39	23	19	12	8	4
80Gy	0	0	0	0	0	0	0



Number of patients at risk							
	0	20	40	60	80	100	120
Extraction	248	196	164	131	97	75	36
No extraction	655	550	453	349	232	147	86

Fig. 3. ORNJ WAFT survival curves for the different covariates considered in the model: (a) gender, (b) $D_{25\%}$ and (c) dental extractions.

extractions were also identified as predictors in the updated NTCP model. Other studies have also reported significant association between ORN and several DVH parameters (e.g., D_{mean} [6], V_{50Gy} and V_{60Gy} [9], V_{44Gy} and V_{58Gy} [33]), as well as with pre-RT dental extractions [34]. Additionally, these risk factors are also noted in the latest ISOO-MASCC-ASCO guidelines [20].

Traditional NTCP models not only rely on binarization of the clinical endpoint (e.g., the presence or absence of ORNJ) but also a fixed-interval truncation of surveillance interval without right-censoring. Thus, while there is abundant suggestion that increased radiation dose increases the risk of ORNJ, there is scant data regarding the relative relationship between pre-therapy dose or clinical factors on time to ORNJ development. Consequently, in this study, we expanded on our existing ORNJ NTCP model [10] to incorporate the temporal information of ORNJ development, by using a novel application of a prediction model incorporating parametric modeling of continuous right-censored time-to-ORNJ prediction.

We have previously shown that prediction models that account for right-censoring can provide differential variable selection compared to categorical classification methods [35]. Notably, the use of right-censor ware TTE models nonetheless also validated our non-right-censored traditional NTCP model, and our results underscored the effect of the risk factors considered. Put simply, these factors not only are correlates of ORNJ but are associated with faster interval of ORNJ development.

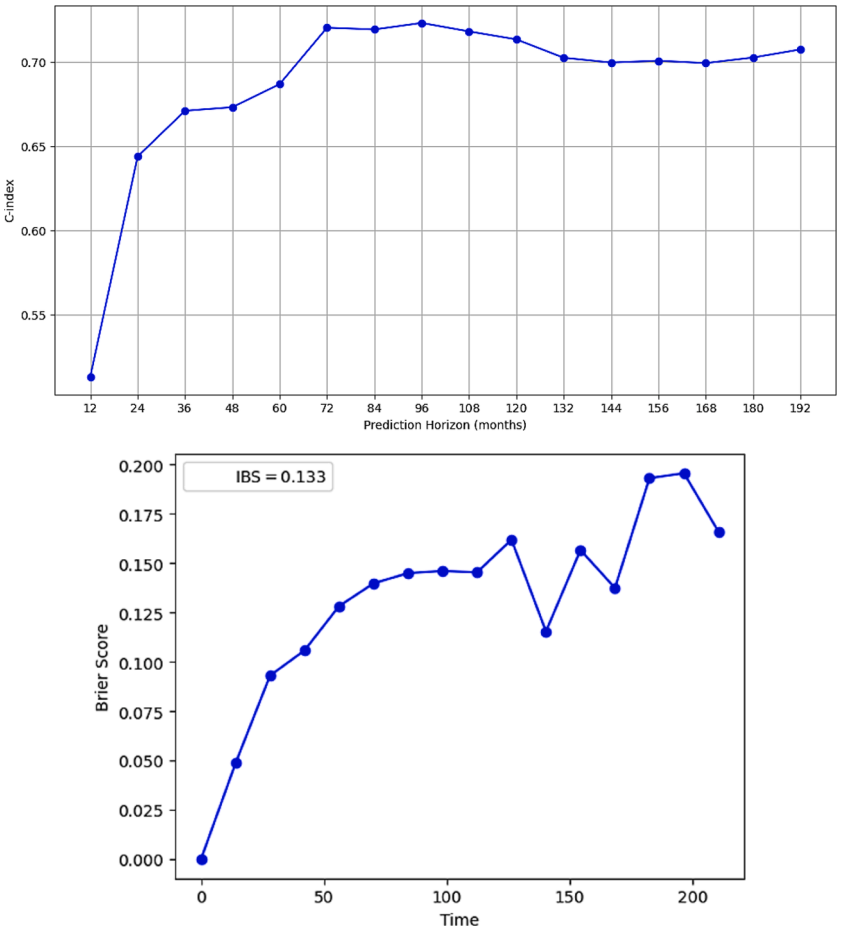


Fig. 4. ORNJ WAFT model performance plots at internal validation. Discrimination performance variation over time is described by the Harrell's C-index (a). Overall model performance over time is described by the Brier score and integrated Brier score (IBS) (b). Model calibration is described by the Distributional calibration curve (c), which represents the computed squared difference between the observed and predicted number of events within different time intervals.

This has important implication for post-RT surveillance in addition to pre-therapy dose reduction strategies. For example, enhanced surveillance imaging methods to monitor progression towards ORNJ, or risk-stratified prevention interventions are potentiated by the proposed model.

Our work has several limitations. By internally and externally validating our model, we have demonstrated its reliability and applicability across diverse patient populations. However, a slight drop in performance was observed in the external validation of the model, most likely introduced by differences in treatment protocols and population characteristics. As opposed to the internal dataset, the external dataset was a matched cohort, with 2:1 control to case matching based on primary tumor site and treatment year, which could have resulted in a reduced variability of clinical characteristics. Moreover, time to event distributions were very different between the training and the external datasets (supplementary Fig. D1): while the model was trained across predictive horizons beyond 204 months, the external test dataset was limited to a maximum of under 100 months. Additional external validation of the WAFT model on a larger and more diverse observational cohort will allow confirmation of the model's generalizability.

Another potential limitation is that the presented results focused on a binary endpoint for ORNJ (i.e., any grade of ORNJ vs. no ORNJ). While this is clinically useful, future studies will expand our work to the prediction of different stages of ORNJ to allow for more personalized intervention and management protocols based on the predicted degree of ORNJ severity risk. For this, in future work, we will aim to re-classify all our ORNJ cases using the ClinRad system in alignment with the latest ISOO-MASCC-ASCO guidelines [20].

Finally, in this study pre-radiotherapy dental extractions were included as a predictor of ORNJ. However, post-radiotherapy dental extractions, despite being a known risk factor [36], were not incorporated into the analysis due to limited documentation at our institution. These extractions frequently occur outside our healthcare system, making reliable data collection challenging. As noted by as van den Bosch et al. [11], there is a significant unmet need for novel higher-dimensional dose-aware toxicity prediction methods to address limitations of standard RT NTCP models as part of an effort to explore non-linear dose–response considerations, and the reality that multiple DVH parameters of the same organ-at-risk (OAR) may be informative have led to applications of "whole DVH" methods [17]. In this study we used dosimetric variables extracted from DVH data. While DVH is still a widely used surrogate of radiation distribution, it does not incorporate spatial information. As a natural next step from the present work, future work will aim to combine the proposed time to ORNJ approach to NTCP modeling with spatial information as the dosimetric risk factor in a spatio-temporal ORNJ prediction model.

In conclusion, our ORNJ Weibull AFT (WAFT) model offers a significant advancement in predicting mandibular ORNJ risk following RT in HNC patients. Predicting the time to ORNJ onset allows for early identification and proactive management of high-risk patients with potential reduction of the severity of ORNJ and improvement of patient outcomes and quality of life.

Data availability statement:

The MDACC deidentified dataset is available in Figshare

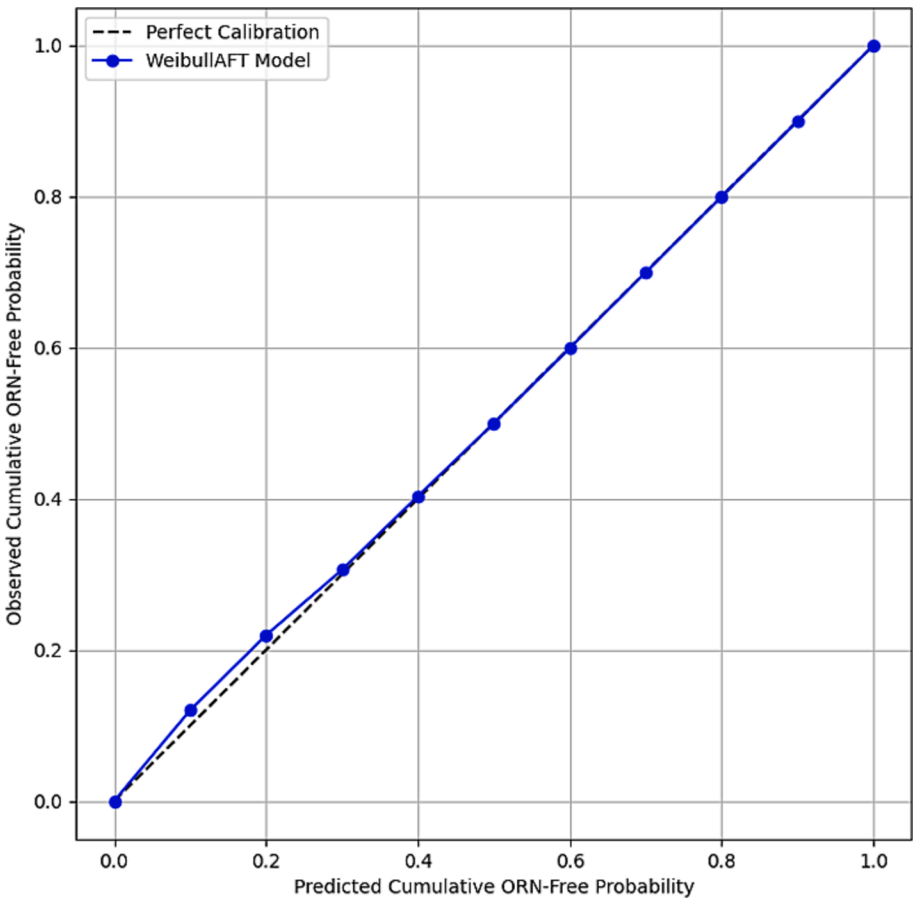


Fig. 4. (*continued*).

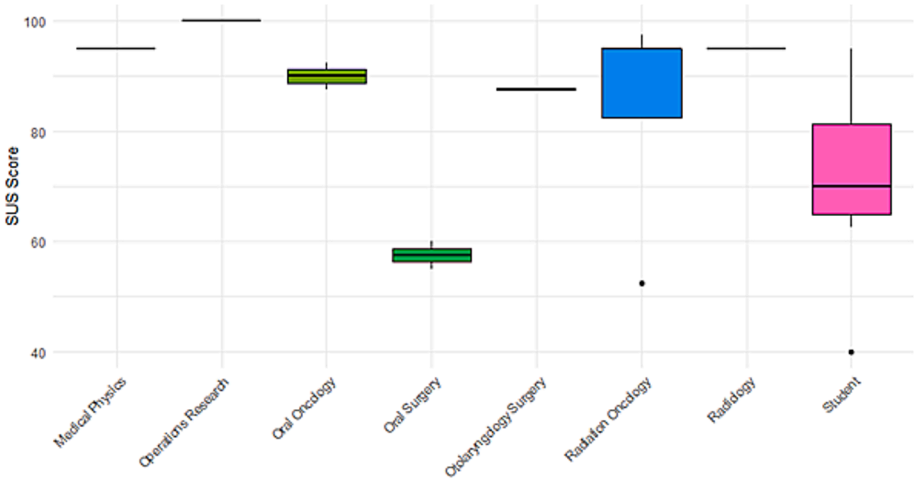


Fig. 5. GUI System Usability Scale (SUS) score distribution by survey participant specialty group.

(https://doi.org/10.6084/m9.figshare.26240435). The GSTT dataset was analyzed onsite using a federated method and, due to GDPR restrictions, cannot be made public. Open access/FAIR reporting of scripts and instructions for the model are available in GitHub (https://github.com/LaiaHV-MDACC/ORN-time-to-event-prediction-modelling).

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT by OpenAI in order to suggest improvements in language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Ethics approval statement

After institutional review board approval (RCR030800), data from a philanthropically funded observational cohort at The University of Texas MD Anderson Cancer Center (Stiefel Oropharynx Cancer Cohort, PA14-0947) were extracted for retrospective acquisition. An external

cohort was obtained retrospectively from the HNC clinical database maintained at GSTT under the Northwest – Haydock Research Ethics committee of the NHS health Research Authority (REC reference 18/NW/0297, IRAS project ID: 231443).

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CDF has received unrelated grant support from Elekta AB and holds unrelated patents licensed to Kallisio, Inc. (US PTO 11730561) through the University of Texas, from which they receive patent royalties. CDF has also received unrelated travel and honoraria from Elekta AB, Philips Medical Systems, Siemens Healthineers/Varian, and Corewell Health. Additionally, CDF has served in an unpaid advisory capacity for Siemens Healthineers/Varian and has served on the guidelines/scientific committee for Osteoradionecrosis for the American Society of Clinical Oncology. VCS is a consultant and equity holder in Femtovox Inc and a consultant for PDS Biotechnology. KAW serves as an Editorial Board Member for Physics and Imaging in Radiation Oncology. The authors declare that no other competing interests exist.

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Appendix A. Supplementary material

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